REMARKS

I. Amendments

Claims 26, 28-30, 32, 33 and 35 were examined. Claims 32 and 33 have been allowed. Claims 26, 28-30 and 35 were rejected. In this response, claims 26, 28-30 and 35 have been amended. The amendments to the claims do not add or constitute new matter. Support for the amended claims may be found throughout the specification and originally filed claims. More particularly, support for claims 26 and 28-29 directed to a targeting construct and methods of producing the targeting construct can be found, for example, at page 12, lines 33-35, at page 18, lines 22-30 and page 59, lines 18-36 through page 60, line 9 of the specification. Additionally, support for claim 30 directed to a method of producing transgenic mice exhibiting a hypoactive phenotype and having a disruption in the melanocyte stimulating hormone receptor gene may be found, for example, at page 18, lines 22-24, page 19, lines 33-35, page 21, lines 11-22, page 39, lines 28-29 and page 59, lines 18-36 through page 60, line 9 of the specification. Lastly, support for claim 35 directed to transformed cells may be found, for example, at page 2, lines 29-35 of the specification. As such, no new matter has been added.

The foregoing amendments are made solely to expedite prosecution of the instant application, and are not intended to limit the scope of the invention. Further, the amendments to the claims are made without prejudice to the pending or now canceled claims or to any subject matter pursued in a related application. Applicants reserve the right to prosecute any canceled subject matter at a later time or in a later filed divisional, continuation, or continuation-in-part application.

Upon entry of the amendment, 26, 28-30, 32, 33 and 35 are pending in the instant application.

II. Rejections

A. Rejection under 35 U.S.C. § 103

Claims 26, 28, 29 and 35 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Mansour *et al.* (1998) *Nature* 336(24):348-352 ("Mansour") in view of Mountjoy *et al.* (1992) *Science* 257:1248-1251 ("Mountjoy") and Adachi *et. al.* (1999) *J. Immunology* 163:3363-3368 ("Adachi"). Applicants respectfully traverse the holding of this rejection.

To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. MPEP §2143.

According to the Office Action mailed November 17, 2002, Mansour describes a targeted disruption of the *hprt* and proto-oncogene *int-2* in mice embryonic stem cells, and subsequent generation of knockout mice. The Office Action asserts that the disclosure of Mansour relates to a general method for isolating embryonic stem cells containing a targeted mutation in an endogenous gene. More particularly, Mansour describes the targeted disruption of the *hprt* gene and the proto-oncogene *int-2* in mouse embryonic stem cells by homologous recombination using targeting constructs specific for these genes. The Examiner admits that Mansour does not teach or suggest a melanocyte stimulating hormone receptor gene, particularly not the melanocyte stimulating hormone receptor gene represented by SEQ ID NO:19 and recited in the pending claims. More particularly, Mansour does not disclose a targeting construct containing a DNA sequence homologous to a melanocyte stimulating hormone receptor gene or methods of producing such a construct as recited in the pending claims.

Mountjoy, as characterized by the Examiner in the previous Office Action, merely describes the cloning of a mouse melanocyte stimulating hormone receptor gene. Accordingly, the nucleotide sequence of a mouse melanocyte stimulating hormone receptor is provided. The reference in no way relates to targeting constructs, particularly targeting constructs for disrupting a melanocyte stimulating hormone receptor gene, or methods of producing such a construct as recited in the pending claims. Applicants submit that Mountjoy does not teach or suggest a targeting construct containing a DNA sequence homologous to a melanocyte stimulating hormone receptor gene represented by SEQ ID NO:19 or methods of producing such a construct as recited in the pending claims. As such, Mountjoy is absent of any teaching or suggestion of disrupting this melanocyte stimulating hormone receptor gene using such a targeting construct, as recited in the pending claims. Thus, Mountjoy fails to make up the deficiencies in Mansour and as such, the presently claimed invention is not obvious.

Adachi, as characterized by the previous Office Action, describes that a melanocyte stimulating hormone receptor may be expressed on a stimulated mast cell line and that the hormone inhibits the release of histamine from mast cells. The Office Action also asserts that Adachi describes that a melanocyte stimulating hormone receptor may be involved in cell proliferation and cytokine production in inflammatory tissue. However, as noted in Applicants' previous response, Adachi does not contain any disclosure related to the specific melanocyte stimulating hormone receptor gene represented by SEQ ID NO:19, and clearly fails to teach or suggest any targeting construct, and particularly not a targeting construct capable disrupting this gene, as is recited in the pending claims. The disclosure in Adachi related to the potential role of α-MSH in inflammatory responses is not sufficient to cure the deficiencies in Mansour and/or Mountjoy, which contain no reference to disruption of the specific gene of the instant invention using the targeting construct as presently claimed. As such, the presently claimed invention is not obvious.

The references, either alone or combined as suggested by the Examiner, clearly fail to teach all of the limitations as recited in the pending claims as is required to establish a prima facie case of obviousness. In any case, in order to expedite prosecution of the instant application, Applicants have amended the pending claims. After the instant amendment, the pending claims recite a targeting construct capable of disrupting a melanocyte stimulating hormone receptor gene represented by the sequence disclosed in SEQ ID NO:19, which targeting construct produces a specific disruption resulting in lack of production of the protein encoded by the sequence represented by SEQ ID NO:19 and hypoactivity in a transgenic mouse whose genome comprises the disruption. The claims, as amended, no longer only recite an "intended use of the knockout construct," which, according to the Examiner, allegedly does not carry patentable weight, but now clearly recite the unexpected result of disruptng the melanocyte stimulated hormone receptor gene produced by the claimed targeting construct, which is a phenotype of hypoactivity in a mouse, as recited in the pending claims. Therefore, the references fail to recite all of the claimed limitations, and thus fail to establish even a prima facie case of obviousness. As such, Applicants submit that the amended claims are not obvious in view of the amendments and remarks set forth above. Accordingly, Applicants respectfully request that the rejection of claims 26, 28, 29 and 35 under 35 U.S.C. § 103 be withdrawn.

B. Rejection under 35 U.S.C. § 112, second paragraph

The Examiner rejected claim 30 under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter regarded as the invention. Applicants respectfully traverse this rejection.

More particularly, the Examiner alleges that claim 30 is incomplete for omitting essential steps, such omission amounting to a gap between steps. The Examiner alleges that this omitted step is "breeding the heterozygous transgenic mouse to obtain homozygous transgenic mouse." Although Applicants disagree that the omission of this step results in a gap between steps, Applicants have amended the claim to recite the step of breeding the heterozygous mouse, as suggested in the Office Action. Accordingly, the rejection under 35 U.S.C. § 112, second paragraph, is no longer relevant, and Applicants request withdrawal of this rejection.

Applicants submit that claims 26, 28-30, 32, 33 and 35, in their current form, are definite and particularly point out and distinctly claim the subject matter regarded as the invention in accordance with 35 U.S.C. § 112, second paragraph.

It is believed that the claims are currently in condition for allowance, and notice to that effect is respectfully requested. The Commissioner is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. 50-1271 under Order No. R-654.

Respectfully submitted,

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